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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,985	09/26/2005	Daria Onichtchouk	18744-0033	4668

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,985	ONICHTCHOUK ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-63* is/are pending in the application.

4a) Of the above claim(s) *46-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 37-63 are pending. Claims 1-36 are canceled.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 1/26/07 is acknowledged. The traversal is on the ground(s) that patentability of the claimed use of a saposin-related product of modulator/effector claimed thereof, is not believed to depend upon the mode of delivery (pharmaceutical composition, implant, gene therapy or cellular therapy). Applicants argue claims 38-51 all depend from claim 37 and therefore, should not be subject to restriction and at most would be a species election. Applicants argue in order for a restriction requirement to be appropriate, there must be a serious burden on the Patent Office to search all the inventions, and the inventions must be independent or distinct as claimed. This is not found persuasive because the restriction requirement of 1/26/07 set forth reasons for independent and distinct inventions, as well as reasons for an undue burden. The response by Applicant does not point out any errors in this reasoning. The restriction election requirement states the methods of delivery are patentably distinct because they require materially distinct and separate means of delivery. Applicant has not rebutted this.

The requirement is still deemed proper and is therefore made FINAL.

Claims 46-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/26/07.

Claims 37-45 are under consideration.

Claim Objections

Claims 37 is objected to because of the following informalities: Claim recite "The use". The article "The" should be replaced by "A". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a use of a saposin-related product and/or a modulator/effector thereof, to promote the protection, survival and/or regeneration of insulin producing cells comprising administration to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector thereof. Embodiments limit the prevention or treatment to type I or LADA or progressed type II

diabetes like for example but not limited to patients suffering from diabetes type I or II or LADA in early stages. Embodiments limit the insulin producing cells to beta cells and further the saposin-related product or a modulator/effector thereof that influences the expression level or function of a saposin-related product is administered to a patient (i) as a pharmaceutical composition e.g. enterally, parenterally, or topically directly to the pancreas; (ii) via implantation of saposin-related protein product expressing cells and/or (iii) via gene therapy.

The specification teaches the induction of differentiation of insulin-producing cells by prosaponin in vitro after exposure of mouse embryonic stem (ES) cells (embryoid bodies) tranduced with the Pax4 gene to the prosaponin (specification examples 10 and 11). The specification also contemplates the therapeutic potential of prosaposin induced insulin-producing cells to improve and cure diabetes can be investigated by transplanting the cells into streptozotocin induced diabetic mice. However, the specification has failed to provide guidance to correlate a use of induction of differentiation of insulin-producing cells by prosaponin in vitro to the use of a saposin-related product and/or a modulator/effector to promote the protection, survival and/or regeneration of insulin producing cells by administering to a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector. The guidance provided by the instant specification fails to correlate the differentiation of insulin producing cells in vitro to the differentiation of insulin producing cells in vivo by administering an effective amount of a saposin-related product and/or a modulator/effector resulting in promoting protection, survival and/or regeneration of

insulin producing cells of a patient in need thereof. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The art teaches that tissue regeneration and restoration of normal tissue function is a major problem in autoimmune diseases like type I diabetes (**Chernajovsky et al,** Nature Reviews, 4: 1-12, 2004) (p 2, 2nd column, last paragraph). Chernajovsky et al, notes that strategies to treat type I diabetes such as surrogate beta cells, have limitations due to the immunogenicity of transgenes and vectors and fate of engineered cells in vivo (p 10, 1st column, 1st paragraph). Chernajovsky further discusses that "A current limitation of most preclinical studies of treatments for autoimmune disease is that immunogenic vectors are often used as proof of concept in animal models. Progress has also been restricted because many studies are short term (in part due to the vector) or have used an acute model of disease, which does not truly reflect the chronic nature of autoimmune diseases in humans. Yet these studies, using numerous targets, have provided strong evidence that local or systemic gene therapy could be a potent method of treatment and warrants further investigation (p 10, 2nd column, 1st paragraph). **Jun et al** (Current Gene Therapy, 5: 249-262, 2005) even after the filing of the instant application notes that studies for regulating the growth and differentiation of islet cells have identified many transcription factors such as Pax4 may play a role in pancreatic development (p 254, 1st column, 1st paragraph), however, there is no satisfactory strategy yet for clinical application to human type 1diabetes (p 254, 2nd column 2nd paragraph). Jun went on to say that more studies are required for the

identification and isolation of beta cell progenitor and/or stem cells, promotion of the proliferation of regenerated or differentiated insulin-producing beta cells, and prevention of immune attack against new beta cells (p 254, 2nd column, 2nd paragraph). Jun concludes that Insulin gene therapy is limited by appropriate insulin production in response to physiological levels of glucose. β cell regeneration is limited by persisting autoimmune attack against newly generated β cells. None of these approaches have yet provided the perfect solution for the cure of type 1 diabetes and are still "work in progress." It is hoped that continuous effort on a variety of potential approaches will offer the best choices for the permanent cure of human type 1 diabetes (p 257, 1st column. Jun also reports even though embryonic stem cells transfected with Pax4 gene, a transcription factor essential for beta cell development and differentiation into insulin-producing cells and normalized blood glucose when transplanted into diabetic mice, however, the report by **Rajagopal et al,** (Science, 299: 363, 2003) does not support beta cell differentiation from embryonic stem cells. Rajagopal reports that differentiated insulin-positive cells were reported to contain 1 μg of insulin per mg of total protein. This is less than 0.02% of the insulin found in the media to which these cells are exposed, raising the possibility that insulin is subsequently cultured in insulin-deficient media lost insulin staining. (This release of absorbed insulin may mimic genuine secretion.) Some absorbed insulin is retained for more than 3 weeks in insulin-deficient media. Therefore, the mere persistence of insulin immunoreactivity in a transplant of ES cell progeny is insufficient evidence of β cell differentiation or function P 363, 1st column last paragraph bridge 2nd column).

The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector resulting in promoting protection, survival and/or regeneration of insulin producing cells of a patient in need thereof as raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of beta cell differentiation by a saposin-related product and/or a modulator/effector is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for promoting protection, survival and/or regeneration of insulin producing cells by a saposin-related product and/or a modulator/effector without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector, particularly type I/II diabetes or LADA , the lack of direction or guidance provided by the specification beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector, particularly type I/II diabetes or LADA , the absence of working examples that correlate to the beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a

modulator/effector, particularly type I/II diabetes or LADA , the unpredictable state of the art with respect to beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector, particularly type I/II diabetes or LADA , and the breadth of the claims directed to all types and stages of daibetes, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Deborah Crouch

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